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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
|-----------------|-------------|----------------------|---------------------|------------------|

10/522,592

01/25/2005

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01/22/2009

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EXAMINER

BHAT, NARAYAN KAMESHWAR

ART UNIT

PAPER NUMBER

1634

MAIL DATE

DELIVERY MODE

01/22/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

| | | | |
|------------------------------|--------------------------------------|--------------------------------------|--|
| Office Action Summary | Application No. 10/522,592 | Applicant(s) MADJAR ET AL. | |
| | Examiner NARAYAN K. BHAT | Art Unit 1634 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 November 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-28 and 33-40 is/are pending in the application.
- 4a) Of the above claim(s) 1-27 and 34-39 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 28,33 and 40 is/are rejected.
- 7) ☒ Claim(s) 40 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

FINAL ACTION

1. This office action is written in reply to applicant's correspondence filed November 6, 2008. Claims 28 and 33 were amended. Claims 29-32 were cancelled. New claim 40 was added. Applicants have amended independent claim with an additional limitation of a dependent claim. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.**
2. Applicants arguments filed on November 6, 2008 have been fully considered and addressed following claim rejections.
3. Claims 1-28 and 33-40 are pending in this application.
4. Claims 1-27 and 34-39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention of group I-IV and VI-VII in the reply filed on October 22, 2007.
5. Claims 28, 33 and 40 are under prosecution.

Declarations

6. Declaration and supporting documents submitted by Applicants on November 6, 2008 to point out references of Niswender et al and Sodhi et al are time consuming and do not provide proportions of the different 5-HT2c-R RNA, whereas the reference of Poyau et al published post filing of the instant application provides the detection of 32 possible 5-HT2c-R mRNA isoforms using primers claimed in claim 28. However, as discussed in the response to remarks section, the declarations and support documents provided are not enough to overcome the rejections set forth in this office action.

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Claim Objections

7. Claim 40 is objected to because of the following informalities: There appears to be typographical error in the phrase “pair of printers is labeled with fluorophores” in line 2. Appropriate correction is required. For compact prosecution, said claim is interpreted as primers are labeled with fluorophores.
8. Previous objections to claims 32 and 33 have been withdrawn in view of cancellation of said claims.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

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11. Claims 28, 33 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stanton et al (USPGPUB NO. US2001/0034023 published Oct. 25, 2001) in view of Larsen et al (Human mutation, 1999, 13, 318-327) and further in view of Gelfand et al (USPN 5,487,902 issued Jul. 30, 1996).

Previous rejections are maintained.

Regarding claims 28 and 40, Stanton et al teaches a SSCP method for obtaining, under given analytical conditions, the editing profile of 5-HT_{2c}-receptor mRNA using a specific tissue sample or using a sample of a population of eukaryotic cells, said method comprises extracting the total RNAs of from eukaryotic cell lines and tissue samples and purifying the RNA by acid- phenol protocol (paragraphs 0973-0974, step 'a' of the instant claim 28).

Stanton et al also teaches the reverse transcription of the RNAs to generate cDNA (paragraph 0974) and further teaches amplifying the cDNA by PCR (paragraph 0975), which generates the double-stranded DNA (step 'b' of the instant claim 28). Stanton et al also teaches the PCR amplification of the DNAs using a pair of primers specific for a particular gene and said primers being labeled with a fluorescent dye, i.e., fluorophore (paragraphs 0085-0088, limitation of claim 40). However it is noted in the SSCP method, Stanton teaches an alternative way to label the PCR product using radioactive isotope (paragraph 0975). Stanton et al also teaches that mRNA is that of 5-HT_{2c} receptor (Table 3, pg. 114, last 5 lines, and paragraph 0114).

Stanton et al are silent about using primer pair represented by SEQ ID NO 36 and 37.

Stanton et al also teaches that the PCR products are produced from the 5' end of the gene (paragraph 0975), thus able to capture all transcripts originating from 5' end of the gene, which may be processed differently at 3' end. The teachings of Stanton et al thus encompass mRNA, which may be edited and primers are chosen so as to amplify all the editing forms potentially present in the RNA extract (step 'c' of the instant claim 28).

Stanton et al are silent about purification and quantifying the PCR product. However, both steps 'c' and 'd' are "where appropriate steps", which are interpreted broadly as optional steps to carry out SSCP.

Stanton et al also teaches denaturation (i.e., dissociation) of the double stranded DNAs to single stranded DNAs by heating followed by abrupt cooling (paragraph 0977, step 'f' of the instant claim 28) and separation of single stranded DNAs by gel electrophoresis (paragraph 0978, step 'g' of the instant claim 28). Stanton et al also teaches obtaining the electrophoretic profile by reading the mobility difference and acquiring data (paragraph 0977-0978). The electrophoretic profile taught by Stanton et al is the editing profile of the claim as defined in the instant specification (See instant specification, USPGPUB, paragraph 0123).

Stanton et al teaches acquisition of the editing profile data in DNA sequencing to catalog sequence variation using the software associated with the fluorescence reader (paragraph 0415). However, Stanton et al are silent about capillary electrophoresis and acquiring fluorescence data associated with a fluorescent reader system in the SSCP method.

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Regarding claim 33, Stanton et al teaches a SSCP method for obtaining, under given analytical conditions, the editing profile and the editing rate of an mRNA which may be edited, using a specific tissue sample or using a sample of a population of eukaryotic cells, characterized in that it comprises the following steps: a) obtaining the electrophoretic profile, i.e., editing profile by means of the SSCP method (Example 13, paragraphs 0970-0978, step 'a' of the instant claim 33). Stanton et al also teaches comparing the sequence variation profile obtained by SSCP method with known variants, i.e., standard profile in the gene corresponding to sequence variation profile for known mRNAs following a drug treatment (paragraph 0114, Example 16, paragraphs 1007-1022, step 'b' of the instant claim 33). Stanton also teaches the sequence variations of a known gene before and after drug treatment (Example 16, paragraphs 1007-1011), thus teaching a ratio of sequence variation ratio of known to new, which is the editing rate as defined in the instant specification (Instant specification, USPGPUB, paragraph 0145). Teachings of Stanton et al thus encompass selecting known editing profile and associating with editing rate (steps 'c' and 'd' of the instant claim 33).

Regarding claim 28, Stanton et al are silent about capillary electrophoresis and acquiring fluorescence data associated with fluorescent reader system in the SSCP method.

However, fluoresce monitoring and capillary electrophoresis were known in the art before the claimed invention was made as taught by Larsen et al, who teaches a high-throughput SSCP analysis by automated capillary electrophoresis and further teaches generating PCR amplified double stranded DNA using fluorescently labeled

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primer (pg. 319, column 2, See PCR amplification section). Larsen et al also teaches separation of single stranded DNAs by capillary electrophoresis (pg. 320, column 1, paragraph 2) and obtaining the electrophoretic profile by reading the fluorescence and acquisition by means of the of the genetic analyzer detection system associated with fluorescence reader (pg. 319, column 1, paragraph 1, pg. 320, column 1, paragraph 2).

Larsen et al also teaches that fluorescent labeling, automated capillary electrophoresis decreases the workload and increases the throughput dramatically compared with analysis by gel electrophoresis (pg. 319, column 1, paragraph 3).

It would be have been prima facie obvious to one having the ordinary skill in the art at the time the invention was made to modify the separation and detection step of SSCP method of Stanton et al with fluorescent labeling and automated capillary electrophoresis method of Larsen et al with a reasonable expectation of success.

One having the ordinary skill in the art would have been motivated to modify the separation and detection step of SSCP method of Stanton et al with the expected benefit of using fluorescent labeling, automated capillary electrophoresis decreasing the workload and increasing the throughput dramatically as compared with analysis by gel electrophoresis as taught by Larsen et al (pg. 319, column 1, paragraph 3), thus avoiding hazardous radioactive isotopes and increasing the throughput of the SSCP detection method of Stanton et al.

Stanton et al teaches a SSCP method to characterize sequence variation in genes comprising 5-HT_{2C} receptor (Example 13, paragraphs 0114, 0970-0978, Table 3, pg. 114, last 5 lines) and further teaches primers are labeled with fluorophores

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(paragraphs 0085-0088). Stanton et al and Larsen et al are silent about primers of SEQ ID NO 36 and 37. However, primers for PCR was known in the art at the time of the claimed invention was made as taught by Gelfand et al, who teaches a process of detecting a target nucleic acid using primers in a PCR amplification assay (column 2, lines 52-67). Gelfand et al. also provides guidance in the choosing of primers: "The primer must be sufficiently long to prime the synthesis of extension products in the presences of the agent for polymerization. The exact length and composition of the primer will depend on many factors, including temperature of the annealing reaction, source and composition of the primer, proximity of the probe annealing site to the primer annealing site, and ratio of primer, probe concentration. For example, depending on the complexity of the target sequence, the oligonucleotide primer are of 15-30 nucleotides and sufficiently complementary to selectively anneal to their respective strands" (column 8 lines 3-34).

It would be have been prima facie obvious to one having the ordinary skill in the art at the time the invention was made to modify the primer for PCR amplification step in the SSCP method of Stanton et al and Larsen et al with the designed primer at any region of the target of Gelfand et al.

Since Gelfand et al provides guidance for designing and selecting the primer any region of the target, one having the ordinary skill in the art would have been motivated to select any number of primers including SEQ ID NOS. 36 and 37 for use in detecting the 5-HT-2C receptor region of defined length during amplification or extension as taught by Gelfand et al (column 7, lines 27-67 and column 8, lines 1-34).

Response to Declarations from the Applicant

12. Declarations and support documents submitted by the Applicant on November 6, 2008 have been fully considered and addressed below.

Applicants summarize the finding of the prior art and further notes that Niswender identifies the proportion of a given site but not the proportion of the different isoforms in which site is edited. Applicants also summarize the finding of Sodhi et al and notes that method of identifying isoforms of 5-HT_{2c} receptor RNA is time consuming and too expensive (Remarks, pg. 20). Applicants also note that using SEQ ID NO 36 and 37 primer pairs of the instant application, Poyau et al detects 32 different isoforms of 5-HT_{2c} RNA (Remarks, pgs. 22 and 23).

Although Applicants summarize their unexpected results, viz., SEQ ID 36 and 37 primers capable of amplifying mRNA and not genomic DNA, discrimination of different forms of 5-HT_{2c} RNA by RT-PCR, SSCP and capillary electrophoresis, claims as written do not encompass the unexpected results. Since Applicants summary of the invention do not commensurate with the scope of the claims as written the declarations and support documents provided are not enough to overcome the rejections set forth in this office action.

Response to remarks from the Applicants

Claim Rejections under 35 U.S.C. § 103(a)

13. Applicant's arguments filed November 6, 2008 have been fully considered but are not persuasive for the following reasons.

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Applicants argue that Larsen et al only describes the use of SSCP-CE for identifying the allelic variant and at most identifies two different cDNA fragments in the sample mixture, whereas 32 isoforms of the 5-HT_{2c} receptor cDNA can be potentially present in the sample mixture (Remarks, pg. 23, last paragraph, pg. 24, and paragraph 1). These arguments are not persuasive, because claims 28, 33 and 40 as recited do not recite the presence of 32 different 5-HT_{2c} receptor cDNA fragments. Furthermore, claims 28, 33 and 40 are rejected under 103(a) using combination of Stanton et al, Larsen et al and Gelfand et al references and not under 35 USC 102 (a, b or e). Stanton et al teaches SSCP method and detects at least 6 different 5-HT_{2c} receptor sequence (Table 3) and Applicant have asserted that Larsen et al teaches SSCP-CE (Remarks, pg. 23, last paragraph). Also, Applicant's arguments are based against the references of Stanton et al or Larson et al or Gelfand et al individually, whereas the rejections are based on combinations of references (See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986)). Since Applicants arguments are based on individual references and presence of 32 different 5-HT_{2c} receptor cDNA fragments, which is not a claimed feature, arguments are not persuasive.

In response to applicant's argument that the references fail to show certain features of applicant's invention (Remarks, pg. 23, paragraph 2), it is noted that the features upon which applicant relies (i.e., 13 different isoforms) are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988

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F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). In the instant case, claims are directed to CE-SSCP method and as described in this office action in section 11, steps 'a' to 'h' recited in the claim 28 are taught by Stanton et al, Larsen et al and Gelfand et al, arguments are not persuasive.

Applicants further argue that Gelfand et al do not remedy the deficiency of Stanton et al and Larson et al (Remarks, pg. 24, and paragraph 3). This argument is not persuasive because Applicant has not traversed the teachings, suggestions and motivations of Gelfand et al

Applicants remaining arguments (Remarks, pg. 24, last paragraph, and pg. 25, first paragraph) are reiterative of the previous arguments and they are not persuasive for the same reasons as described above.

Conclusion

14. No claims are allowed.

15. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the

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shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Narayan K. Bhat whose telephone number is (571)-272-5540. The examiner can normally be reached on 8.30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram R. Shukla can be reached on (571)-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Narayan K. Bhat/

Examiner, Art Unit 1634

/Ram R. Shukla/

Supervisory Patent Examiner, Art Unit 1634